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15 MRT 2005

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The Patent Office

Cardiff Road
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1. Your Reference — **DMK/PB60734P**

2. Patent application number *(The Patent office will fill in this part)* — 0403149.8 — 12 FEB 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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13FE304 E872943-1 D02029
P01/7700 0.00-0403149.8 NONE

Patents ADP number *(if you know it)* 4735870003.

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **MEDICAMENT**

5 Name of your agent *(if you know one)* — **DENISE MCKINNELL**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Description	**6**
Claim(s)	**1**
Abstract	**0**
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Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature **DENISE MCKINNELL** **12 February 2004**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON

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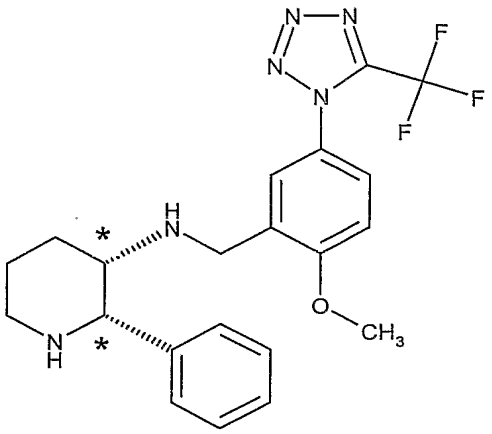
Medicament

This invention relates to the use of the compound [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine and pharmaceutical compositions containing it in the treatment or prevention of social phobia.

International patent application number WO95/08549 describes novel piperidine derivatives. A particularly preferred compound described therein is [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine and it has the following chemical structure (I)

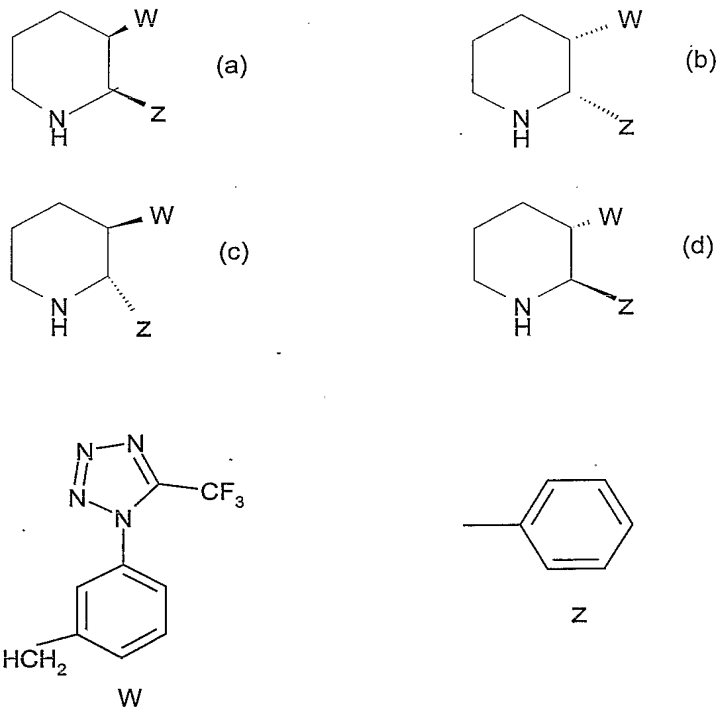


(I)

It will be appreciated by those skilled in the art that the compound of formula (I) contains two chiral centres (shown as * in formula (I)) and thus exists in the form of two pairs of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures.

For example, the compound of formula (I) may be either the cis isomer, as represented by figures (a) and (b), or the trans isomer, as represented by figures (c) and (d), or mixtures thereof.

All of the isomers of the compound of formula (I) represented by the figures (a) to (d) and mixtures thereof including racemic mixtures are included within the scope of the invention.



The compound of formula (I) is preferably in the form of the cis isomer (i.e. as represented by figures (a) and (b)). The 2S, 3S isomer, [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine, (i.e. as represented by figure (b)) is particularly preferred.

Suitable pharmaceutically acceptable salts of the compound of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

A particularly preferred pharmaceutically acceptable salt of the compound of formula (I) for use according to the present invention is the dihydrochloride.

The compound of formula (I) and salts and solvates thereof are described in WO95/08549 as potent and specific NK_1 receptor antagonists.

The compound of formula (I) was initially evaluated for its use in the treatment and prevention of emesis.

The present invention relates to the discovery that the compound of formula (I) or pharmaceutically acceptable salt or solvate thereof is also useful in the treatment of social phobia.

Although certain people may experience anxiety when speaking in front of an audience or at other social gatherings, social phobia occurs when this anxiety actually begins to have a large impact on the individual's professional and personal life. This anxiety may manifest itself prior to, as well as during, a social situation. These anxiety symptoms are associated with changes in brain activity and certain receptors in the brain.

Within the context of the present invention, the term social phobia includes various disease states, including Social Phobia, Generalized, which is classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV), number 300.23. The various forms of the disorders mentioned herein are contemplated as part of the present invention.

In a first aspect thereof, the invention provides the use of the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of social phobia.

In a further aspect thereof, the invention provides the use of the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for the treatment of social phobia.

In a yet further aspect, the invention provides a method of treatment of social phobia which comprises administering to a human in need thereof an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

In a yet further aspect thereof, the present invention provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the treatment or prevention of social phobia.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus, the compound of formula (I) and its pharmaceutically acceptable salts and solvates may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compound of the invention and its pharmaceutically acceptable salts and solvates may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compound of the invention and its pharmaceutically acceptable salts and solvates may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents,

thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compound of the invention and its pharmaceutically acceptable salts and solvates may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compound of the invention and its pharmaceutically acceptable salts and solvates may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compound of the invention and its pharmaceutically acceptable salts and solvates may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compound of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Thus, for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 100 mg e.g. 10 to 50 mg.

The compound of formula (I) may be prepared by the process described in international patent application no. WO95/08549, which is incorporated herein by reference.

Pharmacological Activity

The invention may be illustrated by suitable patient studies. The following example of a suitable patient study is for illustrative purposes and is not intended to limit the scope of the invention in any way, The study was a double-blind, placebo-controlled study of the effect of [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride in patients suffering from social anxiety.

Thirty six patients aged between 19 and 48 meeting the DSM-IV criteria for social phobia (as set out in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association) were selected. Prior to the first Positron Emission Tomography (PET) investigation, patients were marked for severity in triplets, based on the Social Phobia Screening Questionnaire and as far as possible for sex and age. Patients were randomly allocated to one of three groups: NK1-antagonist, selective serotonin reuptake inhibitor (SSRI), or placebo. The NK1-antagonist group received the NK1 antagonist [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride (daily oral dose of 5 mg) and the SSRI group received citalopram (daily oral dose of 40 mg).

After six weeks of treatment, the medication was suspended and patients received follow-up assessments at two and four weeks after the treatment period. The effect of [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride on anxiety symptoms and brain activity in patients diagnosed with social phobia was evaluated using self-report questionnaires (the Social Phobia Scale (SPS), the Social Interaction Anxiety Scale (SIAS), the Personal Report on Confidence as a Speaker (PRCS), the Social Phobia Screening Questionnaire (SPSQ), the Sheehan Disability Inventory (SDI), self-report versions of the Liebowitz Social Anxiety Scale (LSAS-SR) and the Global Assessment of Functioning (GAF) scale), state anxiety measures (the Speilberger state-anxiety inventory (STAI-S), subjective ratings of fear and distress on 0-100 (min-max) scales and heart rate), verbal performance (comparing the number of spoken syllables during the first ten seconds of each videotaped speech) and PET assessments.

Patients with social phobia were significantly improved after short-term treatment with the NK1-antagonist [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride or citalopram and both drugs were generally superior to placebo. The clinical and behavioural effect of [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride was similar to that of citalopram even though it was administered for a shorter period i.e. four as compared to six weeks.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of social phobia.

2. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the treatment of social phobia.

3. A method of treatment of social phobia which comprises administering to a human in need thereof an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

4. Use of a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the treatment of social phobia.

5. Use of a compound of formula (I) according to any of claims 1, 2 or 4 wherein the compound is [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine or a pharmaceutically acceptable salt or solvate thereof.

6. Method according to claim 3 wherein the compound is [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine or a pharmaceutically acceptable salt or solvate thereof.

7. Use according to any of claims 1, 2, 4 or 5 wherein the pharmaceutically acceptable salt is the dichloride.

8. Method according to claim 3 or claim 6 wherein the pharmaceutically acceptable salt is the dichloride.